HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (3), 2012, 253-261**

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF NEW CLASS OF 1-SUBSTITUTED-*N*-(1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)-1*H*-BENZO[*D*][1,2,3]TRIAZOLE-5-CABOXAMIDE DERIVATIVES

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ABSTRACT
A series of 1-substituted-*N*-(1,2,3,4-tetrahydronapthalene-1-yl)-1*H*-benzo[*d*][1,2,3]triazole-5-carmoxamide derivatives(**5a-l**) were synthesized and their antimicrobial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis, Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiellapneumoniae*, *Proteus mirabilis and Candida albicans*was evaluated *in vitro*. It was found that most of the tested compounds especially compounds**5h** and **5k**shown stronger activity to the selected bacteria and fungi. The chemical structuresof the new compounds were confirmed by elemental and spectral (^{1}H NMR, ^{13}C NMR, Mass) analysis

KEYWORDS
Triazole, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Klebsiellapneumoniae, Proteus mirabilis and Candida albicans, antimicrobial activity.

INTRODUCTION

Heterocyclic compounds with nitrogen atoms are considered to be one of the most important antimicrobial drugs used either as single agents or incombination for cancer therapy.[1,2] Recent studyshowed that several benzotriazole and 1,2,4-triazolederivatives represented an interesting class of heterocycle[3] and became the most rapidly expandinggroup of antifungal compounds with the advantageof low toxicity, high oral bioavailability and broadspectrumactivity.[4-6] Moreover, a variety of benzotriazole derivatives have been reported to inhibit the growthof some microorganisms[7]and some benzotriazolederivatives exhibit good pharmacological activities such as analgesic, anti-inflammatory, antifungal, antineoplastic, antiviral, and antihypertensive activities.[8] Inaddition, El-Ashry*et al* also reported that the benzotriazole derivatives used as antioxidants for industrial lubricating oils.[9]

Currently the amide functional group play important role in organic and biological chemistry. Amides are important as pharmaceutical as well as agrochemicals.[10] In general, the formation of amide bond directly from carboxylic acids requires activation of the carboxyl group. Activation of a carboxyl group can be achieved by conversion into more reactive functional groups.[11]

Coupling reagents could be used for *in-situ* activation of the carboxyl group.[12-16] Recently, novel reagents were reported for the synthesis of an amide bond.[17] In the last decades, some phosphonium and uronium salts were used as coupling reagents for the synthesis of peptides.[18-20]Furthermore, antimicrobial peptides are found in most living organisms and have been most interesting compounds due to their structure and unique mode of action different from the most conventional antimicrobials.[21] These peptides exhibit activity against a broad spectrum of microbes but showed fairly low activity. Also several classes of antimicrobial peptides have been studied and their mechanisms of action against several microbes not yet clear and its elucidation would form a sound basis for the further development of new pharmaceutical compounds.[22]In this connection, we have synthesized novelbenzotiazole derivatives (**5a-l**) by the coupling of tetrahydronapthyl aminewithvarious benzotirazolecarboxylic acids. The present study was undertaken with a view to find theefficacy of these benzotirazole derivatives as antimicrobial agents.

EXPERIENTAL

All the reagents and solvents were pure, purchased from commercial sources and were used without further purification unless otherwise stated. Melting points were determined in open capillaries with a "Cintex" melting point apparatus Mumbai, India and were uncorrected. CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 models). ^{1}HNMR spectra were recorded on a Mercury-400 spectrometer in δ ppm using TMS as standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API- 2000, ESI) at 12.5 eV.

General procedure for synthesis of 2

A mixture of 4-fluoro-3-nitrobenzoic (1 eq), amine(1.5eq) and $NaHCO_3$(2.5 eq) in water (20 mL) were heated to 160^{o}C for 1-6 h in a sealed tube. The reaction mixture was cooled to room temperature, poured into 1M HCl and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to obtain compound **2**.(TLC: EOAc:Pet ether; 1:1; R_f: 0.3; Yield: 88-95%). We used the above method for rest of the monomers

General procedure for synthesis of 3

To a solution of Compound **2**(1.0 eq)in EtOH(200 mL) was added palladium on charcoaland the resulting suspension was stirred at room temperature under hydrogen atmosphere for 3-8 h.The reaction mixture was filtered through celite and the solvent was removed under reduced pressure to obtain Compound **3.**(TLC: EOAc:Pet ether; 1:1; R_f: 0.5; Yield: 60-85%).We used the above method for rest of the monomers

General procedure for synthesis of 4

To a solution of Compound 3 (1.0 eq) in AcOH(20 mL) was added sodium nitrite (1.5 eq) and stirred at room temperature for 12-24 h.Reaction mixture was quenched with water and extracted with EtOAc (2 x 50 mL), washed with brine, dried over sodium sulphate and concentrated under reduced pressure to obtain Compound4. (TLC: EOAc:Pet ether; 7:1; R_f: 0.3; Yield: 82-93%).Crude product was used as such in the next step without further purification. We used the

above method for rest of the monomers. Crude product was used as such in the next step without further purification.

General procedure for synthesis of 5

To a solution of Compound **4**(1.0 eq)in DMF (10 mL) was added Tetrahydronapthyl amine (1.2 eq),EDC.HCl (2.0 eq),HOBt(2 eq) and Et_3N (2.5 eq). The resultant reaction mixture was stirred for 12-24 h at room temperature.Reaction mixture was quenched with water, extracted with EtOAc, washed with water, dried over sodium sulphate and concentrated under reduced pressure to obtain the crude compound **5.** The crudecompound was recrystallised from DCM and pentane. (TLC;EOAc:Pet ether; 1:1; R_f: 0.4; Yield: 75-86%).We used the above method for rest of the monomers.

1-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide (5a)

IR (KBr, cm^{-1}): 1303 (N-C), 1472 (C=C), 1548 (N=C), 1685 (N=N); 1710 (C=O), 1448, 2869, 2913 (CH_2), 3031 (arom. CH), 3369 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.65 (q, CH_2); 1.98 (t, *J* =7.6, CH_2); 2.75 (t, *J* =6.8, CH_2); 4.35 (s, CH_3); 4.99 (t, *J* = 12, CH); 6.98 (d, *J* = 7.2, 2 arom. H); 7.09 (d, *J* = 6.6, 2 arom. H); 8.52 (d, *J* = 12.0, 2 arom. H); 8.96 (s, arom. H); 12.52 (s, 1 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.6 (CH_2); 28.2(CH_2); 30.6 (CH_2); 35.5 (CH_3); 52.6 (CH); 115.1 (CH); 123.7 (CH); 126.8 (2CH); 127.6 (CH); 129.6 (CH); 131.5 (CH); 133.8 (C); 135.6 (C); 136.9 (C); 138.7 (C); 162.4 (C=O). MS: 307.5 (M^++1). Anal.calc. for $C_{18}H_{18}N_4O$ (306.50): C 70.59, H 5.95, N 18.28; found: C 70.54, H 5.98, N 18.21.

***1-ethyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5b).**

IR (KBr, cm^{-1}): 1308 (N-C), 1465 (C=C), 1544 (N=C), 1686 (N=N); 1702 (C=O), 1456, 2862, 2916 (CH_2), 3038 (arom. CH), 3375 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.35 (t, *J* = 2.4, CH_3), 1.53 (q, CH_2); 1.81 (t, *J* =4.4, CH_2); 2.77 (t, *J* =6.0, CH_2); 3.96 (q, CH_2); 5.06 (t, *J* = 7.2, CH); 6.76 (d, *J* = 6.8, 2 arom. H); 7.11 (d, *J* = 6.8, 2 arom. H); 8.54 (d, *J* = 7.4, 2 arom. H); 8.84 (s, arom. H); 11.93 (s, 1 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.6 (CH_3); 19.8 (CH_2); 25.7 (CH_2); 29.3 (CH_2); 47.5 (CH_2); 55.6 (CH); 118.1 (CH); 122.7 (CH); 126.7 (2CH); 128.2 (CH); 130.5 (CH); 132.1 (CH); 133.7 (C); 135.2 (C); 136.3 (C); 139.3 (C); 161.4 (C=O). MS: 321.4 (M^++1). Anal.calc. for $C_{19}H_{20}N_4O$ (320.33): C 71.25, H 6.31, N 17.48; found: C 71.34, H 6.28, N 17.51.

***1-propyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5c)**.

IR: 1303 (N-C), 1472 (C=C), 1548 (N=CH), 1648 (N=N); 1705 (C=O), 1448, 2869, 2913 (CH_2), 3038 (arom. CH), 3347 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (t, CH_3), 1.46 (q, CH_2); 1.76 (q, CH_2); 1.96 (t, *J* =2.8, CH_2); 2.76 (t, *J* =7.6, CH_2); 4.56 (s, CH_3); 4.98 (t, *J* = 2.4, 6.4, CH); 6.78 (d, *J* = 6.8, 2 arom. H); 7.11 (d, *J* = 6.4, 2 arom. H); 8.58 (d, *J* = 7.2, 2 arom. H); 8.92 (s, arom. H); 11.52 (s, 1 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.56 (CH_3), 19.5 (CH_2); 23.8 (CH_2); 27.6(CH_2); 31.3 (CH_2); 49.5 (CH_2); 53.2 (CH); 113.3 (CH); 122.4 (CH); 125.2 (2CH); 126.7 (CH); 130.7 (CH); 132.9 (CH); 133.2 (C); 135.6 (C); 137.9 (C); 139.2 (C); 160.3 (C=O). MS: 334 (M^+). Anal.calc. for $C_{20}H_{22}N_4O$ (334.24): C 71.82, H 6.65, N 16.78; found: C 71.79, H 6.68, N 16.71.

***1-cyclopropyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5d).**IR: 1313 (N-C), 1482 (C=C), 1567 (N=CH), 1642 (N=N); 1702 (C=O), 1443, 2867, 2918 (CH_2), 3054 (arom. CH), 3362 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 0.53 (q, $2CH_2$);

1.54 (q, CH_2); 1.82 (q, CH_2); 1.99 (t, *J* =6.4, CH_2); 2.68 (m, CH); 2.78 (t, *J* =8.4, CH_2); 5.02 (t, *J* = 9.2, 7.6, CH); 6.84 (d, *J* = 6.8, 2 arom. H); 7.08 (d, *J* = 8.2, 2 arom. H); 8.34 (d, *J* = 7.8, 2 arom. H); 8.82 (s, arom. H); 10.58 (s, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 1.4 (2CH2); 20.2 (CH_2); 23.4 (CH_2); 28.3(CH_2); 38.4 (CH); 56.4 (CH); 109.7 (CH); 120.5 (CH); 124.8 (2CH); 126.3 (CH); 130.4 (CH); 133.7 (CH); 136.4 (C); 139.2 (C); 140.7 (C); 145.3 (C); 162.6 (C=O). MS: 333.1 (M^++1). Anal.calc. for $C_{20}H_{20}N_4O$ (332.43): C 72.28, H 6.05, N 16.88; found: C 72.29, H 6.08, N 16.85.

***1-cyclopentyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5e).**IR: 1321 (N-C), 1458 (C=C), 1563 (N=CH), 1644 (N=N); 1715 (C=O), 1440, 2861, 2919 (CH_2), 3037 (arom. CH),3352 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.38 (m, 2CH_2), 1.42 (q, CH_2); 1.73 (q, 2CH_2); 2.03 (t, *J* =4.8, CH_2); 2.65 (t, *J* =6.8, CH_2); 3.86 (q, CH); 5.06 (t,*J* = 6.4, CH); 6.88 (d, *J* = 6.2, 2 arom. H); 7.10 (d, *J* = 8.2, 2 arom. H); 8.45 (d, *J* = 12.0, 2 arom. H); 8.94 (s, arom. H); 10.26 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5 (CH_2); 26.6 (2CH_2); 29.7 (CH_2); 30.5 (CH_2); 32.4 (2CH_2); 53.7 (CH); 118.3 (CH); 120.6 (CH); 124.3 (2CH); 127.8 (CH); 130.2 (CH); 132.1 (CH); 133.0 (C); 134.9 (C); 137.0 (C); 138.8 (C); 162.4 (C=O). MS: 361.2 (M^++1). Anal.calc. for $C_{22}H_{24}N_4O$ (360.54): C 73.32, H 6.73, N 15.58; found: C 73.29, H 6.68, N 15.61.

***1-cyclohexyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5f).**IR: 1308 (N-C), 1452 (C=C), 1567 (N=CH), 1649 (N=N); 1704 (C=O), 1443, 2865, 2923 (CH_2), 3048 (arom. CH), 3347 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.32 (m, 3CH_2), 1.48 (q, CH_2); 1.77 (q, 2CH_2); 2.01 (t, *J* =2.7, CH_2); 2.60 (t, *J* =12.8, CH_2); 3.78 (q, CH); 5.13 (t,*J* = 7.4, CH); 6.83 (d, *J* = 6.2, 2 arom. H); 7.05 (d, *J* = 8.2, 2 arom. H); 8.46 (d, *J* = 12.0, 2 arom. H); 8.92 (s, arom. H); 4.25 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.6 (CH_2); 26.4 (3CH_2); 29.2 (CH_2); 31.2 (CH_2); 33.8 (2CH_2); 54.2 (CH); 111.4 (CH); 120.5 (CH); 124.8 (2CH); 128.6 (CH); 130.8 (CH); 132.0 (CH); 133.8 (C); 134.1 (C); 137.3 (C); 138.2 (C); 164.4 (C=O). MS: 375.1 (M^++1). Anal.calc. for $C_{23}H_{26}N_4O$ (374.14): C 73.77, H 7.03, N 14.98; found: C 73.77, H 7.01, N 14.86.

***1-phenyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5g).** IR (KBr, cm^{-1}): 1308 (N-C), 1488 (C=C), 1581 (N=C), 1645 (N=N); 1710 (C=O), 2261 (CN), 2863, 2914 (CH_2), 3057 (arom. CH),3336 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.78 (q, CH_2); 2.08 (t, *J* =2.0,2.4, CH_2); 2.84 (t, *J* =8.7, CH_2); 5.05(t, *J* = 1.6, 2.0 CH); 6.85 (d, *J* = 9.6, 2 arom. H); 7.12 (d, *J* = 6.4, 2 arom. H); 7.46 (t, *J* = 8.0, 7.6, arom. H); 7.56 (t, *J* = 4.0, 4.4, 2 arom. H); 7.84 (d, *J* = 10.4, arom. H); 8.37 (d, *J* = 7.6, arom. H); 8.48 (d, *J* = 7.6, arom. H); 8.65 (s, arom. H); 8.80 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.7 (CH_2); 30.3 (CH_2); 32.3 (CH_2); 53.2 (CH); 109.4 (CH); 121.3 (CH); 125.8 (CH); 126.2 (CH); 127.4 (2CH); 128.3 (CH); 129.3 (CH); 132.8 (CH); 133.2 (C); 134.1 (C); 135.8 (C); 137.4 (C); 148.6 (C); 168.1 (C=O). MS: 369 (M^++1). Anal.calc. for $C_{23}H_{20}N_4O$ (368.24): C 74.88, H 5.45, N 15.19; found: C 74.84, H 5.48, N 15.13.

***1-(4-nitrophenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5h).** IR (KBr, cm^{-1}): 1311 (N-C), 1487 (C=C), 1584 (N=C), 1654 (N=N); 1712 (C=O), 2263 (CN), 2867, 2910 (CH_2), 3056 (arom. CH),3347 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.84 (q, CH_2); 2.10 (t, *J* =2.8, CH_2); 2.88 (t, *J* =8.8, CH_2); 5.07(t, *J* = 2.5, CH); 6.91 (d, *J*

= 9.6, 2 arom. H); 7.12 (d, *J* = 6.4, 2 arom. H); 7.85 (d, *J* = 12.4, 2 arom. H); 7.94 (d, *J* = 4.0, 2 arom. H); 8.34 (d, *J* = 7.2, arom. H); 8.41 (d, *J* = 7.6, arom. H); 8.62 (s, arom. H); 8.87 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.8 (CH_2); 29.4(CH_2); 31.9 (CH_2); 52.7 (CH); 115.3 (CH); 122.1 (CH); 123.4 (CH); 124.3 (CH); 126.3 (2CH); 128.3 (2CH); 129.1 (2CH); 135.2 (C); 136.1 (C); 136.9 (C); 138.3 (C); 147.4 (C); 168.3 (C=O). -MS: 414.1 (M^++1). Anal.calc. for $C_{23}H_{19}N_5O_3$ (413.51): C 66.82, H 4.65, N 16.94; found: C 66.84, H 5.61, N 16.93.

***1-(3-nitrophenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5i).** IR (KBr, cm^{-1}): 1310 (N-C), 1485 (C=C), 1574 (N=C), 1652 (N=N); 1705 (C=O), 2264 (CN), 2862, 2911 (CH_2), 3057 (arom. CH),3352 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.88 (q, CH_2); 2.15 (t, *J* =2.0, 2.4, CH_2); 2.85 (t, *J* =8.9, CH_2); 5.11 (t, *J* = 2.4, 2.8, CH); 6.95 (d, *J* = 9.8, 2 arom. H); 7.10 (d, *J* = 6.8, 2 arom. H); 7.28 (t, *J* = 4.8,5.0, arom. H); 7.45 (d, *J* = 12.4, arom. H); 7.52 (d, *J* = 4.8, arom. H); 8.24 (d, *J* = 7.6, arom. H); 8.45 (d, *J* = 7.6, arom. H); 8.68 (s, 1 arom. H); 8.74 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5 (CH_2); 29.6(CH_2); 31.1 (CH_2); 52.9 (CH); 116.3 (CH); 122.4 (CH); 123.8 (CH); 125.3 (CH); 126.7 (2CH); 128.4 (2CH); 129.5 (2CH); 135.6 (C); 136.2 (C); 136.7 (C); 138.8 (C); 147.3 (C); 168.5 (C=O). MS: 414.2 (M^++1). Anal.calc. for $C_{23}H_{19}N_5O_3$ (413.51): C 66.83, H 4.64, N 16.95; found: C 66.84, H 5.61, N 16.93.

***1-(2-nitrophenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5j).** IR (KBr, cm^{-1}): 1312 (N-C), 1483 (C=C), 1571 (N=C), 1653 (N=N); 1702 (C=O), 2267 (CN), 2865, 2916 (CH_2), 3057 (arom. CH),3356 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.85 (q, CH_2); 2.16 (t, *J* =2.0, 2.4, CH_2); 2.83 (t, *J* =8.9, CH_2); 5.14(t, *J* = 2.4, 2.8, CH); 6.99 (d, *J* = 9.8, 2 arom. H); 7.12 (d, *J* = 6.8, 2 arom. H); 7.23 (t, *J* = 4.8,5.0, arom. H); 738 (t, *J* = 2.8,2.4, arom. H); 7.47 (d, *J* = 12.4, arom. H); 7.56 (d, *J* = 4.8, arom. H); 8.28 (d, *J* = 7.6, arom. H); 8.44 (d, *J* = 7.6, arom. H); 8.63 (s, 1 arom. H); 8.77 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.5 (CH_2); 29.7(CH_2); 31.6 (CH_2); 52.9 (CH); 117.2 (CH); 122.8 (CH); 124.8 (CH); 125.7 (CH); 126.8 (2CH); 128.6 (2CH); 129.3 (2CH); 135.9 (C); 136.1 (C); 136.6 (C); 137.6 (C); 147.6 (C); 168.9 (C=O). MS: 414.1 (M^++1). Anal.calc. for $C_{23}H_{19}N_5O_3$ (413.51): C 66.84, H 4.65, N 16.98; found: C 66.84, H 5.61, N 16.93.

***1-(2,2,2-trifluoroethyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5k).** IR (KBr, cm^{-1}): 854 (C-F); 1311 (N-C), 1465 (C=C), 1588 (N=C), 1664 (N=N); 1700 (C=O), 1442, 2864, 2915 (CH_2), 3032 (arom. CH),3364 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.68–1.72 (q, CH_2); 1.99–2.02 (t, *J* =2.8, CH_2); 2.78–2.82 (t, *J* =7.2, CH_2); 4.62 (s, CH_2); 5.05-5.12 (t, *J* = 2.8, CH); 6.92 (d, *J* = 8.4, 2 arom. H); 7.13 (d, *J* = 7.2, 2 arom. H); 8.32 (d, *J* = 6.8, 2 arom. H); 8.65 (s, arom. H); 4.54 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.2 (CH_2); 27.6 (CH_2); 30.5 (CH_2); 53.8 (CH); 62.4 (CH_2); 107.9 (C); 117.8 (CH); 121.4 (CH); 123.5 (2CH); 125.2 (CH); 126.2 (CH); 130.1 (CH); 132.4 (C); 132.6 (C); 136.5 (C); 137.2 (C); 168.4 (C=O). MS: 375.1 (M^++1). Anal. calc. for $C_{19}H_{17}F_3N_4O$ (374.55): C 60.99, H 4.59, F 15.25, N 14.95; found: C 60.94, H 4.58, F 15.29, N 14.93.

***1-(cyanomethyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-benzo[d][1,2,3]triazole-5-carboxamide*(5l).** IR (KBr, cm^{-1}): 1308 (N-C), 1485 (C=C), 1582 (N=C), 1646 (N=N); 1703 (C=O), 2265 (CN), 2863, 2917 (CH_2), 3052 (arom. CH),3336 (NH).^{1}H-NMR (400 MHz, $CDCl_3$): 1.75 (q, CH_2); 2.01 (t, *J* =2.2, CH_2); 2.82 (t, *J* =8.7, CH_2); 4.93 (s, CH_2); 5.02 (t, *J* = 1.6,

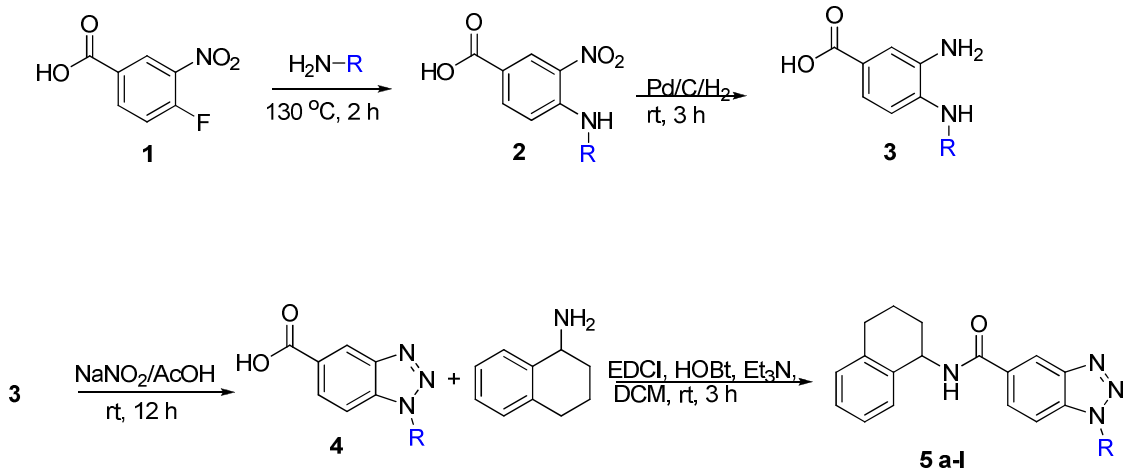
CH); 6.98 (d, *J* = 9.6, 2 arom. H); 7.10 (d, *J* = 6.4, 2 arom. H); 8.35 (d, *J* = 7.6, 2 arom. H); 8.44 (s, arom. H); 4.89 (brs, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.4 (CH_2); 26.3 (CH_2); 30.3 (CH_2); 49.4 (CH_2); 55.2 (CH); 117.9 (CN); 119.8 (CH); 121.2 (CH); 123.4 (2CH); 126.3 (CH); 128.3 (CH); 132.8 (CH); 134.2 (C); 135.1 (C); 136.3 (C); 137.2 (C); 167.3 (C=O). MS: 332.2 (M^++1). Anal.calc. for $C_{19}H_{17}N_5O$ (331.24): C 68.89, H 5.18, N 21.13; found: C 68.84, H 5.18, N 121.13.

Antibacterial Activity

In vitro antibacterial activities of new compounds against *S. aureus*, *S. epidermidis*, *E. faecalis*, *P. aeruginosa*, *E. coli*, *K. pneumonia*, *P. mirabilis* and antifungal activities against *C. albicans*were investigated. Minimum inhibitory concentrations (MICs) of compounds were determined by microbroth dilution technique as described by the Clinical and Laboratory Standards Institute.[23] Serial two fold dilutions ranging from 5000 to 4.8 µg/mL were prepared in Mueller-Hinton broth (MHB) for bacteria and RPMI-1640 medium for yeast. Each well was inoculated with 50 µL of a 4 to 6 hour broth culture that gave a final concentration of 5 × 105 cfu/mL for bacteria and 5 × 103 cfu/mL for yeast in the test tray. The trays were covered and placed in plastic bags to prevent evaporation. The trays containing MHB were incubated at 35 °C for 18–20 h, those containing RPMI-1640 medium at 35 °C for 46–50 h. The MIC was defined as the lowest concentration of compound producing complete inhibition of visible growth. Amikacin and fluconazole were used as reference antibiotics for bacteria and yeast, respectively. The MIC values of the amikacin and fluconazole were within the accuracy range in CLSI throughout the study.[24] The MIC values of the compounds are given in **Table 1**.

RESULTS AND DISCUSSION

We report here the synthesis, characterization and antimicrobial screening of 1-substituted-*N*-(1,2,3,4-tetrahydronapthalene-1-yl)-1*H*-benzo[*d*][1,2,3]triazole-5-carmoxamide derivatives **5**, a medicinally useful scaffold, for the first time with 80% overall yield over five steps from the commercially available 4-fluoro-3-nitrobenzoic acid 1. The synthetic route is outlined in Scheme 1. First, the substitution of aryl fluoride occurred readily in refluxingethanol, THF, or water with a primary amine to give a series of4-amino-3-nitrobenzoic acids (**2)** in near-quantitative yield. Reduction of the nitro phenyl moiety occurred readily underan atmospheric pressure of hydrogen with activated palladiumon carbon to give the bisamine (**3**), which could be isolated butwas best reacted immediately with sodium nitrite in acetic acidto form the benzotriazole (**4**) in good yield. Finally to get the desired products (**5a-l**) by coupling with tetra hydronaphthalene aminein the presence of 20%dimethylformamide (DMF)–CH_2Cl_2 at 0 ^oC.The amides thus obtained were characterized by ^{1}H NMR, ^{13}C NMR, and massspectral data. The ^{1}H NMR spectral data of compounds **5a–l**showed a broadsinglet of a NH proton of amide linkage from d 4.35 to 12.00 ppm.^{13}C NMR spectra of the compounds **5a–l**alsoshowed the signals of a, b, and c carbons in the spectra. Furthermore, the carbonylcarbon of amide linkage appeared downfield from d 167.0 to 168.9, confirmingformation of the amide derivatives.



Scheme-I

5a R = CH_3 **5g** R = C_6H_5

5b R = CH_3CH_2 **5h** R = 4-$NO_2C_6H_4$

5c R = $CH_3CH_2CH_2$ **5i** R = 3-$NO_2C_6H_4$

5d R = Cyclopropyl **5j** R = 2-$NO_2C_6H_4$

5e R = Cyclopentyl **5k** R = Trifluoroethyl

5f R = Cyclohexyl **5l** R = Cyanomethyl

Biological screening

All the synthesized pteridine derivatives **5a-l** were investigated for their *in vitro* antibacterial activities against three Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*) and four Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiellapneumoniae*, *Proteus mirabilis*). The antifungal activity was tested against a yeast *Candida albicans***.**

All the biological results of the tested compounds are given in **Table 1.** As seen in Table 1, all of the new compounds, **5h,** and **5k** possessed excellent activity against all organismswith MIC values of between 150–250µg/mL. Among the tested compounds, only **5i**showed perfect activity with the MIC value of 250-350µg/mL against all organisms. The compound, **5j** and **5l** also showed excellent antibacterial activity against all organisms except *K.neumonia.*

Table 1.*in vitro* antibacterial and antifungal activity of the synthesized compounds **5a-l.**

	MIC values (µg/mL)							
	Microorganisms							
Compound	***S. aureus***	***S. epidermidis***	***E. faecalis***	***P. aeruginosa***	***E.coli***	***K. neumoniae***	***P.mirabilis***	***C.albicans***
5a	500	550	500	600	500	500	650	500
5b	*	*	500	550	600	550	650	600
5c	*	550	600	*	500	500	500	550
5d	500	550	550	500	500	*	500	320
5e	400	*	400	450	450	550	400	*
5f	300	350	450	300	*	340	450	300
5g	400	450	*	425	400	450	450	450
5h	150	200	250	150	150	150	200	150
5i	300	350	300	300	350	300	350	250
5j	300	400	455	350	300	*	350	250
5k	150	200	250	150	150	150	200	150
5l	300	350	450	450	450	*	300	250
amikacin	100	150	100	150	100	150	150	-
fluconazole	-	-	-	-	-	-	-	100

*Not found

REFERENCES

1. K.Katarzyna, N.Zelika,Z.Justyna,*Bioorg.Med. Chem.*12, 2617 (2004).
2. H-Q.Li, C.Xu, H-S.Li, Z-P.Xiao, L.Shi,H-L.Zhu,*Chem. Med. Chem.*, 2, 1361**(**2007).
3. G.Biagi, I.Giorgi, O.Livi, V.Scartoni, P. L.Barili,V.Calderone,*Il Farmaco*56, 827 (2001).
4. G.Scapin, S. B.Patel, J. W.Becker, Q.Wang, C.Desponts, D.Waddleton, K.Skorey, W.Cromlish, C.Bayly,M.Therien, J. Y.Gauthier, C-S.Li, C. K.Lau,C.Ramachandran, B. P.Kennedy,E.Asante-Appiah,*Biochemistry* 42, 11451 (2003).
5. C.Antonio, P.Michele, B.Gianpiero, B.Bernardetta,M.Marta,L.Roberta,*Il Farmaco* 59, 637 (2004).
6. L-Z.Xu, F-F.Jian, H-R.Gao,C-Y.Chong,*Chin. J. Chem*. 21, 1615 (2003).
7. M. B.Bushuev, A. V.Virovets, Y.Garcia,C.Gieck,L. A.Sheludyakova, V.N.Ikorskii, W.Tremel, P.Gutlich,L. G.Lavrenova,*Polyhedron*21, 797 (2002).
8. K. Katarzyna, A. Najda, J. Zebrowska, L. Chomicz, J. Piekarczyk, P. Myjak, and M.Bretner, *Bioorg. Med. Chem.*, **13,** 3601 (2005).
9. El-S.H. El-Ashry, M.E. El-Rafey, M.H. El-Nagdi, H.H. Abou-Elnaga,W.M.A. Bakry, Y.M. Boghdady, *Lubrication Science* 18, 109 (2006).
10. D.B. Bailey, I.D. Doller, M.M. Morgen, in: A.R.Katritzky, D. Meth-Cohn, C.W. Rees, (Eds.),*Comprehensive Organic Functional GroupTransformation*, Elsevier, Cambridge, pp. 257-307(1995)
11. a) G. Benz, in: B.M. Trost, I. Fleming, (Eds.),C*omprehensive Organic Synthesis,* Vol. 6,

PergamonPress, Oxford, (1991), pp. 381-417; b) R.C. Larock,*Comprehensive Organic Transformations*, 2nd ed., JohnWiley, New York, (1999).
12. (a) J.C. Sheehan, G.P. Hess, *J. Am .Chem. Soc*.77,1067 (1955). (b) J.D. Wilson, C.F. Hobbs, H. Wengaten, *J. Org. Chem.*35, 1542 (1970). (c) T. Yasuhara, Y. Nagaka, A.K. Tomiok, *J. Chem. Soc.Perkin Trans.* 1, 2091 (2000). (d) C. Burnell-Gurty, E.J. Roskamp, *Tetrahedron Lett*.34,5193 (1993). (e) P. Froyen, *Synth. Commun*. 25, 959 (1995).
13. (a) D.O. Jang, D.J. Park, J. Kim, *Tetrahedron Lett.*40, 5323 (1999). (b) K. Ishihara, S. Oharsa, H. Yamamato, *J. Org. Chem.*61, 4196 (1996). (c) J.D. Thorsen, T.P. Andersen, V. Pedersen, B. Yde, S.Laweson, *Tetrahedron*41, 5633 (1985). (d) Y. Basel, A. Hassner, *Tetrahedron Lett.*43,2529 (2002). (e) K. Wakasugi, A. Nakamura, A. Isda, Y. Nishii, N.Nakatani, S. Fukushima, Y. Tanabe, *Tetrahedron*59, 5337 (2003).
14. (a) G.A. Olah, S.C. Narang, A. Garciluna, *Synthesis*661 (1980). (b) K.S. Keshavamurthy, Y.D. Vanker, D.N. Dhar,*Synthesis*, 506 (1982).
15. A. Khalafi-Nezhad, A. Parhami, M.N. Soltani-Rad, A.Zarea, *Tetrahedron Lett.*46, 6879**(**2005).
16. M.A. Bailen, R. Chinchilla, D.J. Dodsworth, C. Najera,C. *Tetrahedron Lett.*41, 9809 (2000).
17. a) X. Wu, L. Hu, *Tetrahedron Lett*. 46, 8401 (2005); b)A. Rimola, S. Tosoni, M. Sodupe, P. Ugliengo,*Chemical Physiscs Letters*,408, 295 (2005); c) A.Novak, L.D. Humphreys, M.D. Walker, S. Woodward,*Tetrahedron Lett.*47, 5767 (2006); d) Z. Ruan, R.M.Lawrence, C.B. Cooper, *Tetrahedron Lett.*47,7649 (2006).
18. L.A. Carpino, *J. Am. Chem. Soc.*115, 4397 (1993).
19. R. Knorr, A. Trzeciak, W. Bannwarth, D. Gillessen,*Tetrahedron Lett.*30, 1927**(**1989).
20. a) O. Marder, F. Alberchio, *ChimicaOggi* (ChemistryToday) 21, 6 (2003); b) P.L. Williams, F. Alberchio, E.Giralt, Chemical Approaches to the Synthesis ofPeptides and Proteins, CRC Press, New York, (1997); c)N. Sewald, H.D. Jakubke, Peptides: Chemistry andBiology, John Weily-VCH, Weinheim, (2003.)
21. Michael Z, *CurrOpinImmunol.,* l4**,** 3 (1992).
22. Michael Zasloff, *Nature*, 415, 389 (2002).
23. (a) Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, 7th ed.; Approved Standard M7-A7; CLSI: Wayne, PA, USA, (2006).(b) Clinical and Laboratory Standards Institute (CLSI). *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard–Second Edition*; M27-A2; CLSI: Wayne, PA, USA, (1997.)
24. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: 7th Informational Supplement*; M100-S20; CLSI: Wayne, PA, USA, (2010).

Received on April 30, 2012.